JUL 18 2001

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Form PTO-1390 (REV. 11-2000) U S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C.

ATTORNEY'S DOCKET NUMBER
26979-0002 US

U.S. APPLICATION NO. (If known, see 37 CFR 1.5)
Not Yet Assigned 09/889687

INTERNATIONAL APPLICATION NO	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/AU00/00025	January 18, 2000	January 18, 1999

TITLE OF INVENTION
PROTECTING GROUPS FOR CARBOHYDRATE SYNTHESIS

APPLICANT(S) FOR DO/EO/US
DEKANY, Gyula, PAPAGEORGIOU, John, BORNAGHI, Laurent & Francois

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.
4. ☐ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☒ is attached hereto (required only if not communicated by the International Bureau).
   b. ☐ has been communicated by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☒ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 20 below concern document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment.
14. ☐ A SECOND or SUBSEQUENT preliminary amendment.
15. ☐ A substitute specification.
16. ☐ A change of power of attorney and/or address letter.
17. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
18. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
19. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
20. ☐ Other items or information:

JC17 Rec'd PCT/PTO 18 JUL 2001

U.S. APPLICATION NO. (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
Not Yet Known 09/889687	PCT/AU00/00025	26979-0002 US

21. ☒ The following fees are submitted:

BASIC NATIONAL FEE (37 CFR 1.492(a)(1) – (5)):

	CALCULATIONS	PTO USE ONLY
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and international Search Report not prepared by the EPO or JPO.......... **$1000.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO.......... **$860.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO.......... **$710.00**		
International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4).......... **$690.00**		
International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4).......... **$100.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$1,000	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	$	
Total claims	11 - 20 =	0	x **$18.00**	$	
Independent claims	1 - 3 =	0	x **$80.00**	$	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ **$270.00**	$	
TOTAL OF ABOVE CALCULATIONS =				$500	
x Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2. +				$500	
SUBTOTAL =				$500	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				$	
TOTAL NATIONAL FEE =				$	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR) 3.28, 3.31)). **$40.00** per property +				$	
TOTAL FEES ENCLOSED =				$500	
				Amount to be refunded:	$
				charged:	$

a. ☒ a check in the amount of $ 500 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. 08-1641 in the amount of $____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 08-1641. A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public **Credit card information should not be included on this form**. Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

Date: July 18, 2001

SEND ALL CORRESPONDENCE TO

William Schmonsees

Heller Ehrman White & McAuliffe LLP

275 Middlefield Road

Menlo Park, CA 94025-3506

Main: (650) 324-7000 Fax: (650) 324-0638

SIGNATURE

NAME: William Schmonsees

REGISTRATION NUMBER: 31,794

09/889687
JC17 Rec'd PCT/PTO 18 JUL 2001

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of	Examiner: Not Assigned
DEKANY *et al.*	Group Art Unit: Not Assigned
Serial No: Not Yet Assigned	Customer No.: 25213
Filed: July 18, 2001	
For: **PROTECTING GROUPS FOR CARBOHYDRATE SYNTHESIS**	**PRELIMINARY AMENDMENT**
Docket No.: 26979-0002 US	

Express Mail Label No.: EL912433811US
Mailed in Palo Alto, CA on: July 18, 2001

BOX PATENT APPLICATION
Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Please preliminarily amend the above application as indicated below.

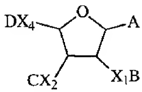
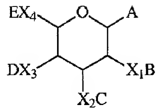
IN THE CLAIMS

Please cancel claims 1-11.

Please add new claims 12-22.

CLAIMS

12. A universal monosaccharide building block of General Formula I or General Formula II

I II

in which,

A is a leaving group selected from the group consisting of -SR; where R is alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkenyl, substituted alkenyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, halogen; trichloroacetimidoyl-; sulphoxide; and -O- alkenyl;

X_1, X_2, and X_3 are independently selected from H, O, N, or N_3, with the proviso that only one of X_1, X_2, and X_3 may be H, N or N_3 in any molecule;

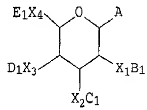
X_4 is H, $-CH_2O$, $-CH_2N$, $-CH_3$, $-CH_2N_3$ or -COO-, with the proviso that X_4 may only be H, $-CH_2N$, $-CH_3$ or CH_2N_3 when none of X_1 to X_3 is H; and

B, C, D and E are different, and are selected from protecting groups which can be cleaved orthogonally in any order,

and in which,

B or C or D or E is absent if the corresponding X_1 to X_3 is H or N_3, or if the corresponding X_4 is H, $-CH_3$ or $-CH_2N_3$.

13. A monosaccharide building block according to claim 12, which is a compound of General Formula III



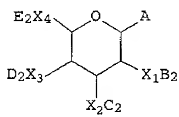
III

in which,

A, X_1, X_2, X_3 and X_4 are as defined for General Formulae I and II, and

B_1, C_1, D_1, and E_1 are orthogonal carbohydrate protecting groups selected from protecting group sets 1, 2, 6 and 8 as herein defined.

14. A monosaccharide building block according to claim 12, which is a compound of General Formula IV



IV

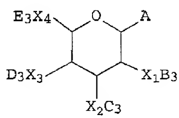
in which,

A, X_1, X_2, X_3 and X_4 are as defined for General Formulae I and II, and

B_2, C_2, D_2 and E_2 are selected from the members of protecting group set 1, and in themselves constitute an orthogonal set.

15. A monosaccharide building block according to claim 14, in which the members of protecting group set 1 are levanoyl, chloroacetate, *p*-methoxybenzyloxycarbonyl and 2-trimethylsilylethylcarbonate.

16. A monosaccharide building block according to claim 12, which is a compound of General Formula V



V

in which,

A, X_1, X_2, X_3 and X_4 are as defined for General Formulae I and II, and

B_3, C_3, D_3 and E_3 are an orthogonal set of protecting groups selected from amongst the members of set 1 and from the remaining orthogonal sets.

17. A method of synthesis of a molecule selected from the group consisting of glycoconjugates of non-carbohydrate molecules, neo-glycoconjugates and oligosaccharides, comprising the step of using a monosaccharide building block according to claim 12.

18. A method according to claim 17, in which the molecule comprises one or more compounds in which substituents are linked to a pyranose or furanose ring.

19. A method according to claim 17, in which the molecule comprises a sugar analogue.

20. A method according to claim 18, in which the molecule comprises a sugar analogue.

21. A method according to claim 17, in which the synthesis is carried out in solution.

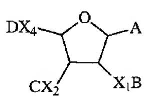
22. A method according to claim 17, in which the synthesis is carried out on a solid-phase support.

IN THE SPECIFICATION

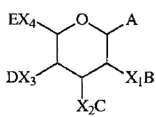
Please add the following paragraph before the paragraph at page 2, line 24:

--Orthogonal protecting strategies and conditions are reviewed in the textbook, "Protecting Groups in Organic Synthesis", by Green and Wicks (3rd edition).

Please replace the figures I and II on page 4 with the following amended figures I and II:



I



II

Please replace the lines 27-31, page 4 with the following rewritten lines:

Docket No. 26979-0002 US

--X_1, X_2, and X_3 are independently selected from H, O, N, or N_3, with the proviso that only one of X_1, X_2, and X_3 may be H, N, or N_3 in any molecule;

--X_4 is H, $-CH_2O$, $-CH_2N$, $-CH_3$, $-CH_2N_3$ or $-COO-$, with the proviso that X_4 may only be H, $-CH_2N$, $-CH_3$ or $-CH_2N_3$ when none of X_1 to X_3 is H; and

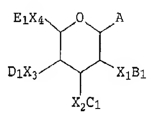
Please replace the paragraph beginning at page 5, line 1 with the following rewritten lines:

--B, C , D, and E are different, and are selected from protecting groups which can be cleaved orthogonally in any an order, and

in which

--B or C or D or E is absent if the corresponding X_1 to X_3 is H or N_3, or if the corresponding X_4 is H, $-CH_3$ or $-CH_2N_3$.

Please replace the figure III on page 7 with the following amended figure III:

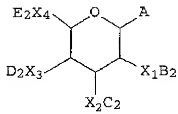


III

Please replace the lines 2-3, page 8 with the following line:

--A, X_1, X_2, X_3 and X_4 are as defined for General Formulae I and II, and

Please replace the figure IV on page 8 with the following amended figure IV:

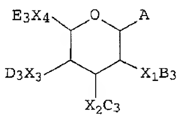


IV

Please replace the lines 14-15, page 8 with the following line:

--A, X_1, X_2, X_3 and X_4 are as defined for General Formulae I and II, and

Please replace the figure V on page 8 with the following amended figure V:



V

Please replace the lines 2-3, page 9 with the following line:

--A, X_1, X_2, X_3 and X_4 are as defined for General Formulae I and II, and

Please replace line 16, page 24 with the following rewritten line:

-- **glucopyranoside (24)**

Please replace line 9, page 29 with the following rewritten line:

-- **acetyl-1-thio-β-D-galactopyranoside (31)**

The applicant wishes to change the order in which the inventors are named to the following order:

DEKANY, Gyula
PAPAGEORGIOU, John
BORNAGHI, Laurent Francois

Applicant submits that the pending claims are directed to allowable subject matter, and respectfully requests consideration and allowance of the application. No new matter is added by the amendments, because the amended claims find support in the application as filed. Entry of the amendment and allowance of the claims are requested.

Respectfully submitted,

By:____________________
William Schmonsees
Registration No. 31,794

Heller Ehrman White & McAuliffe LLP
275 Middlefield Road
Menlo Park, CA 94025
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PROTECTING GROUPS FOR CARBOHYDRATE SYNTHESIS

This invention relates to methods of synthesis of glycoconjugates, and in particular to orthogonally protected carbohydrate building blocks. The invention provides collections of orthogonally protected monosaccharides as universal building blocks for the synthesis of glycoconjugates of non-carbohydrate molecules, neo-glycoconjugates and oligosaccharides. This orthogonal protection strategy allows for the specific deprotection of any substituent on the saccharide ring, and greatly facilitates targeted or library-focused carbohydrate related syntheses.

BACKGROUND OF THE INVENTION

Oligosaccharides are important components of a variety of different types of biological molecules, and are involved in antigenic recognition and cell-cell interactions. In many cases, bio-molecules require conjugation with a carbohydrate component in order to be fully functional. In order to enable investigation of the biological function, and to exploit the exquisite biochemical and antigenic specificity of oligosaccharides, it is essential to have access to highly defined, specific synthetic oligosaccharides. Therefore achieving efficient, cost-effective synthesis of oligosaccharides and glycoconjugates by either solution or solid phase methods is of the utmost importance.

This task is enormously complicated by the complexity of oligosaccharides. Because of the number of sites which can carry substituents, and the number of possible ways in which two saccharide molecules can be linked, the number of permutations is enormously high.

In naturally-occurring oligosaccharides D-glucose, D-galactose L-fucose, D-mannose, D-glucosamine and D-galactosamine are among the most common sugar residues. To construct oligosaccharides and carbohydrate conjugates

using these sugars, current methodologies require long, protracted syntheses, involving synthesis of as many as one hundred different specially-protected sugar donors in order to cover adequately all the possible permutations of glycosidic link formation (*eg.* 1-3, 1-4), link type (*eg.* α or β) and to include all possible branching points in the oligosaccharide.

Orthogonal protection of bi-functional molecules has been a widely used technique in organic chemistry, which provided general building blocks for selected syntheses. However, orthogonal protection in the case of molecules with a greater degree of functionalisation is quite rare. Our technology involves penta-functional monosaccharide building blocks, which require a much higher level of chemical specificity to attain the appropriate orthogonality.

Orthogonal protection has been defined by Merrifield as follows:

> "The principle of orthogonal stability requires that only those protecting functions should be used that can be cleaved under different reaction conditions without affecting the other functions present" (Merrifield, 1977)

Although the use of orthogonal protection would greatly facilitate carbohydrate related synthesis, there has been limited success in devising suitable protecting groups and methods.

Wong *et al.* synthesised a universal building block with chloroacetyl, *p*-methoxybenzyl, levulinyl and *tert*-butyldiphenylsilyl protecting groups, selectively removable with sodium bicarbonate, trifluoroacetic acid, hydrazine and hydrogen fluoride-pyridine respectively, on a galactopyranose ring with an aryl-thio leaving group at the glycosidic position. This building block was used solely to synthesise a 6-hexanate glycoside. The subsequent recombinant oligosaccharide library formation focused on using the 6-hexanate derivatised building block which

exhibits only four degrees of orthogonality (Wong *et al*, 1998).

Similarly Kunz and coworkers synthesised an orthogonally protected D-glucopyranose derivative, but synthetic manipulations were only performed on the aglycon. These authors describe orthogonal protection of hydroxyl groups on a monosaccharide linked at C1 via a thioglycoside group to a solid support or to a succinimide moiety. In this case the protecting groups are acetyl or methyl at C2, allyl at C3, ethoxyethyl at C4, and tert-butyldiphenylsilyl at C6. The thioglycoside anchor functionalized in the side-chain is stated to be crucial. Again there is no suggestion that this protection system can be used for substituted sugars. Kunz's orthogonally-protected building block was not used for glycosylation or construction of glycoconjugates or neo-glycoconjugates, by directly attaching functionalitites to the pyranose ring (Wunberg *et al.* 1998).

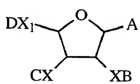
In our earlier International Patent Applications No. PCT/AU97/00544, No. PCT/AU98/00131 and No. PCT/AU98/00808, we described protecting and linking groups which enabled oligosaccharides and aminooligosaccharides to be synthesised using solid phase methods of the type which for many years have been used in peptide synthesis. In addition the protecting groups, described therein were useful for solution-phase synthesis. The entire disclosures of these specifications are incorporated herein by this reference.

We have now devised new types of building blocks which greatly facilitate the synthesis of oligosaccharides and glycoconjugates, using orthogonally-protected saccharide building blocks with five degrees of othogonality. These building blocks contain a leaving group or latent leaving group at the glycosidic position, and another four orthogonally-protected functional groups around the carbohydrate ring.

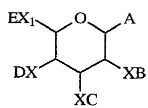
Using our approach with six universal building blocks based on six of the most common naturally occurring sugars, any one of the one hundred sugars referred to above may be quickly synthesised in a facile manner, using simple, well-known protecting group chemistry. The years of work and complex protection strategies required to produce these one hundred building blocks by previously-available methods can be avoided by use of our six universal building blocks, which do not require a high level of skill to use, and enable one to achieve the synthesis of a specific desired oligosaccharide or glycoconjugate much faster and more efficiently than previously possible.

SUMMARY OF THE INVENTION

In its most general aspect the invention provides a universal monosaccharide building block of General Formula I or General Formula II



I



II

in which

A is a leaving group, including but not limited to groups such as -SR; where R is alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, halogen; trichloroacetimidoyl-; sulphoxide; -O-alkenyl;

X is hydrogen, O, N or N_3;

X_1 is hydrogen, $-CH_2O-$, $-CH_2NH-$, $-CH_3$, $-CH_2N_3$ or -COO-; and

B, C, D and E are any protecting groups which can be cleaved orthogonally.

It will be appreciated that as a consequence of stoichiometry and valence bond theory B, C, D and E are absent when X is hydrogen or N_3 and E is absent when X_1 is hydrogen, CH_3 or N_3.

The following non-limiting sets have been designated as orthogonal to each other on the basis of their cleavage conditions. A protecting group is classified in a particular set according to its lability to the cleavage conditions for a particular set and its stability to the cleavage conditions required for the removal of those groups in the remaining sets. Each set is to be taken to include, but is not be limited, by the members thereof.

Of the sets defined, set 1, the 'Base Solvolysis' set, is of particular importance, because in addition to the fact that the members of this set are considered to be orthogonal to the members of the remaining sets, some members of this set are also considered to be orthogonal to each other. Where this is the case, the alternative condition of cleavage that provides orthogonality is specified in brackets following the listing of the protecting group.

1. <u>Base Solvolysis</u>

a) for hydroxy protection:

acyl-type protecting groups, *eg.* chloroacetate (also thiourea-sensitive)
bromoacetate (also pyridine-sensitive)
carbonates, *eg.* Alloc (Pd^0)
Fmoc (β-elimination)
Troc
p-nitrophenylsulphonylethyloxy carbonyl)
levanoyl (also hydrazine sensitive)

b) for amino protection:

Dde, Wow (primary amine-sensitive)
tetraphthaloyl
dichlorophthaloyl
2,5-dimethyl-pyrroyl (primary amine-sensitive)
benzyloxycarbonyl
pentenyl

2. <u>Fluoride Ion-Sensitive</u>
for hydroxy protection:

t-butyldiphenylsilyl
triisopropylsilyl
trimethylsilylethyl
triphenylsilylethyl
(all cleavable with HF/Pyridine)

3. <u>Reduction-Sensitive</u>

trifluoromethyl
trichloromethyloxymethyl
trichloromethyloxycarbonate
(all cleavable with zinc/acetic acid)

4. <u>β-Elimination-Sensitive, Base-Labile Protecting Groups</u>

ethoxyethyl
cyanoethyl
NSC (p-nitrobenzyl-sulphonylethyloxycarbonyl)
p-nitrobenzyl-sulphonylethyl

5. <u>Hydrogenolysis-Sensitive Protecting Groups</u>

naphthylmethyl
substituted naphthylmethyl

6. <u>Oxidation-Sensitive Protecting Groups</u>:

p-methoxybenzyl
3,4-dimethoxybenzyl
2,4,6-trimethoxybenzyl
3,4-methylenedioxybenzyl
acylamidobenzyl
azidobenzyl
p-azido-m-chlorobenzyl

7. <u>Allylic Protecting Groups</u>

Cleavable with Pd^0 complexes

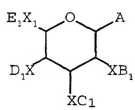
8. <u>Photolabile Protecting Groups</u>:

o-nitrobenzyloxycarbonate
o-nitrobenzyl
dinitrobenzyl
2-oxo-1,2-diphenylethyl

9. <u>Protecting Groups Removable by Relay Deprotection</u>

methylthioethyl
acyloxybenzyl
benzylthioethyl.

In one preferred embodiment, the invention provides a compound of General Formula III



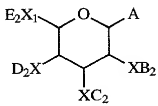
III

in which

A, X and X_1 are as defined for General Formulae I and II, and

B_1, C_1, D_1 and E_1 are orthogonal carbohydrate protecting groups (*ie.* an orthogonal set) selected from protecting group sets 1, 2, 6 and 8.

Another preferred embodiment provides a compound of General Formula IV



IV

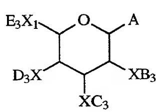
in which

A, X and X_1 are as defined for General Formulae I and II, and

B_2, C_2, D_2 and E_2 are selected from the members of protecting group set 1, and in themselves constitute an orthogonal set, for example the carbohydrate-protecting groups levanoyl (ammonia-labile), chloroacetate (thiourea-labile), *p*-methoxybenzyloxycarbonyl (oxidation-labile) and 2-trimethylsilylethylcarbonate (fluoride ion-labile).

This embodiment provides universal building blocks with protecting groups selected from the protecting groups of set 1.

In a third preferred embodiment the invention provides a compound of General Formula V



V

in which

A, X and X_1 are as defined for General Formula I and II, and

B_3, C_3, D_3 and E_3 are an orthogonal set of protecting groups selected from amongst the members of set 1 and from the remaining orthogonal sets.

This embodiment provides orthogonally protected building blocks, the protecting group constituents of which may be selected from within set 1 and from the remaining sets.

It will be clearly understood that the invention is not limited to use with monosaccharides, but is also applicable to any compound in which substituents are linked to a pyranose or furanose ring, such as sugar analogues.

For the purposes of this specification it will be clearly understood that the word "comprising" means "including but not limited to", and that the word "comprises" has a corresponding meaning.

For the purposes of this specification "orthogonal cleavage" is defined as the regioselective cleavage of a hydroxy or amino protecting group from a carbohydrate, in which the cleavage conditions do not compromise the stability of the other protecting or functional groups on the molecule. Such cleavages can be effected in any order of priority. "Cleaved orthogonally" and "orthogonal cleavage" are taken to be synonymous.

DETAILED DESCRIPTION OF THE INVENTION

Abbreviations used herein are as follows:

Alloc	Allyloxycarbonyl
Bn	Benzyl
Bu	Butyl
DCM	Dichloromethane
Dde	*N*-1-(4,4-Dimethyl-2,6-dioxocyclohexylidene)ethyl

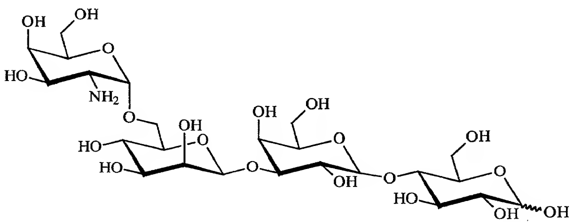
Dde-OH	6-Hydroxy-6-(4,4-dimethyl-2,6-dioxocyclohexyl-idene)ethyl
DMAP	*N,N'*-Dimethylaminopyridine
DMF	*N,N'*-Dimethylformamide
DMTST	Dimethyl(methylthio)sulphoniumtrifluoromethane-sulphonate
EEDQ	1-isobutyloxycarbonyl-2-isobutyloxy-1,2-dihydro-quinoline
EtOAc	Ethyl acetate
EtOH	Ethanol
FAB-MS	Fast atom bombardment mass spectrometry
HRMS	High resolution mass spectrometry
Fmoc	Fluoromethoxycarbonyl
MBHA	Methyl benzyhydryamine resin
Me	Methyl
MeOH	Methanol
NCS	*p*-Nitrobenzyl-sulphonylethyloxycarbonyl
NMR	Nuclear magnetic resonance
ODmab	4-{*N*-[1-(4,4-dimethyl-2,6-dioxocyclohexylidene)-3-methylbutyl]-amino}benzyl alcohol
PEG	Polyethylene glycol
tBu	Tertiary-butyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
Troc	2,2,2-Trichloroethoxycarbonyl

The invention provides universal building blocks, which are useful in the solution and solid phase synthesis of oligosaccharides. The reaction scheme for synthesis of each target molecule is designed so as to specify the orthogonally-protected functional groups which must be freed for glycosylation, and those which need to be capped with a protecting group such as benzyl, benzoyl, or another such group which remains uncleaved until the end of the synthesis, in order to avoid competition during glycosylations later in the synthesis.

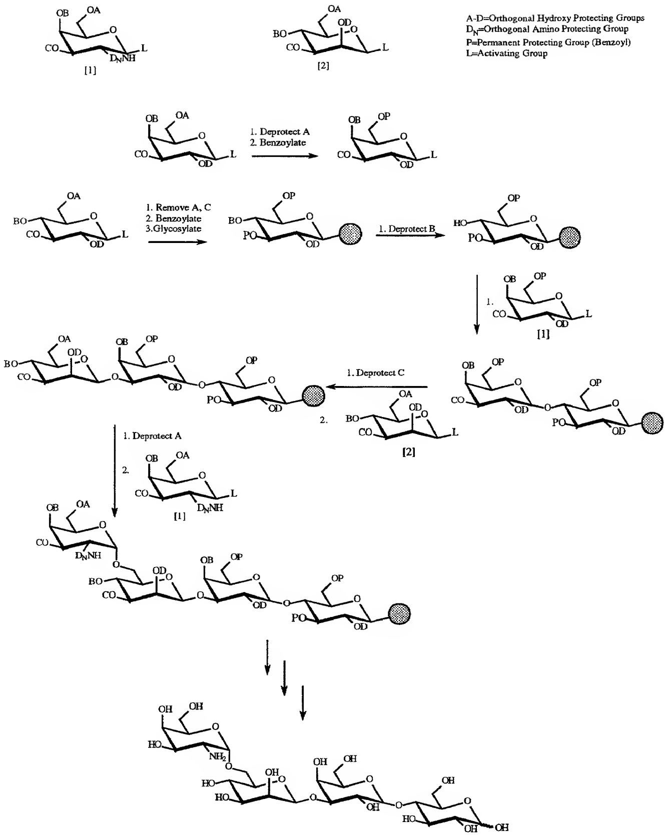
When participation during the glycosylation reaction is required, the 2-hydroxyl is selectively deprotected and re-protected with a benzoyl group which, again, remains until the completion of the synthesis. In the case of 2-deoxy 2-aminosugars, if participation or stereoselectivity is required the Dde group might be removed and replaced with a tetrachlorophthaloyl or 2,5-dimethylpyrrole group.

Example 1 Synthesis of an Exemplary Tetrasaccharide

A strategy for synthesis of the tetrasaccharide of formula VI is set out in Scheme 1.

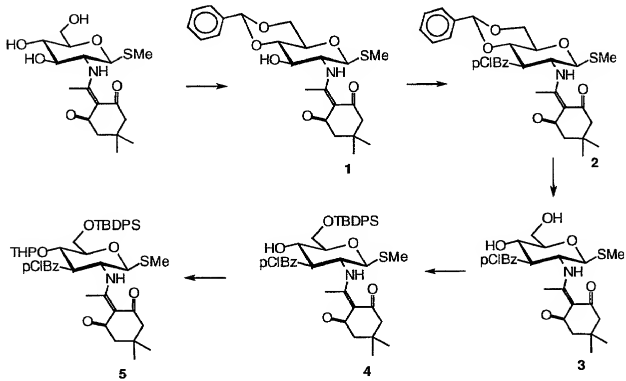


VI


A-D=Orthogonal Hydroxy Protecting Groups
D_N=Orthogonal Amino Protecting Group
P=Permanent Protecting Group (Benzoyl)
L=Activating Group
[1]
[2]
1. Deprotect A
2. Benzoylate
1. Remove A, C
2. Benzoylate
3.Glycosylate
1. Deprotect B
1. Deprotect C
1. Deprotect A

In solution phase, protecting groups A and C from the first sugar residue of the target molecule (residue [4]) are selectively removed, and the sites capped by a permanent protecting group, *eg*. benzoyl group. The residue is then coupled to the resin, followed by selective removal of protecting group B. In solution phase, protecting group A from sugar residue [3] is selectively removed, and the site is capped by a permanent protecting group. Residue [3] is then linked to the resin-bound sugar residue via a glycosylation reaction. Protecting group C from the new disaccharide is removed, and residue [2] is linked via a glycosylation. Protecting group A is finally selectively removed to regenerate the 6-hydroxyl group, which is linked with residue 1.

Example 2 Synthesis of an Orthogonally Protected Thioglycoside Building Block, Methyl 6-O-(t-butyldiphenylsilyl)-3-O-(p-chlorobenzoyl)-2-deoxy-2-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethylamino]-4-O-tetrahydropyranyl-1-thio-β-D glucopyranoside (5)



Methyl 4,6-O-benzylidene-2-deoxy-2-[1-(4,4-dimethyl-2,6dioxocyclohex-1-ylidene)ethylamino]-1-thio-β-D glucopyranoside (1)

A mixture of methyl 2-deoxy-2-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethylamino]-1-thio-β-D glucopyranoside (20 g, 54 mmol), α,α-dimethoxytoluene (9.78 g, 64 mmol) and p-toluenesulphonic acid (50 mg) in dry acetonitrile (100 mL), was stirred at 60°C for 2 hours. The reaction mixture was cooled to room temperature and adjusted to pH 7 with the addition of triethylamine. The solvent was removed *in vacuo*, the residue was taken up in CH_2Cl_2 (200 ml), washed with brine (50 ml), with water

(50 ml) and dried over $MgSO_4$. The organic phase was concentrated to give a yellow solid, methyl 4,6-O-benzylidene-2-deoxy-2-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethylamino]-1-thio-β-D glucopyranoside (24.5 g, 98%).

Methyl 4,6-O-benzylidene-3-O-(p-chlorobenzoyl)-2-deoxy-2-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethylamino]-1-thio-β-D glucopyranoside (2)

A mixture of methyl 4,6-O-benzylidene-2-deoxy-2-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethylamino]-1-thio-β-D-glucopyranoside (**1**)(6.3 g, 13.5 mmol), p-chlorobenzoylchloride (2.6 ml, 20 mmol) and 4-dimethylaminopyridine (2.44 g, 40 mmol) in dry 1,2-dichloroethane (100 ml), was stirred at room temperature overnight. The resultant suspension was filtered, the filtrate diluted with chloroform (100 ml) and washed with diluted brine (3 x 50 ml, H_2O/Brine, 2/1). The organic phase was dried over $MgSO_4$ and the solvent removed *in vacuo* to give yellow solid. The residue chromatographed EtOAc/Hexane 1:1 as the mobile phase to give methyl 4,6-O-benzylidene-3-O-(p-chlorobenzoyl)-2-deoxy-2-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethylamino]-1-thio-β-D-glucopyranoside (**2**)(6.4 g, 80%).

Methyl 3-O-(p-chlorobenzoyl)-2-deoxy-2-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethylamino]-1-thio-β-D glucopyranoside (3)

A mixture of methyl 4,6-O-benzylidene-3-O-(p-chlorobenzoyl)-2-deoxy-2-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethylamino]-1-thio-β-D

glucopyranoside (**2**) (2.51 g, 4.20 mmol) and 50% aqueous solution of tetrafluoroboric acid (1 ml) in acetonitrile (25 mL), was stirred at room temperature for 2 hours. The pH was adjusted to 7 with the addition of triethylamine and the resultant suspension concentrated. The residue was crystallised from diisopropyl ether-ethyl acetate to give methyl 3-O-(p-chlorobenzoyl)-2-deoxy-2-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethylamino]-1-thio-β-D glucopyranoside (**3**) (1.7 g, 79%).

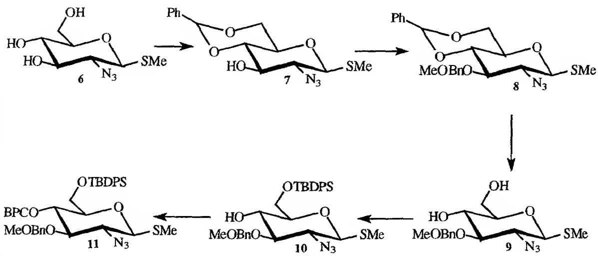
Methyl 6-O-(t-butyldiphenylsilyl)-3-O-(p-chlorobenzoyl)-2-deoxy-2-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethylamino]-1-thio-β-D glucopyranoside (4)

A mixture of methyl 3-O-(p-chlorobenzoyl)-2-deoxy-2-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)-ethylamino]-1-thio-β-D-glucopyranoside (**3**) (1.00 g, 1.95 mmol), t-butyldiphenylsilylchloride (536 mg, 1.95) and 4-dimethylaminopyridine (238 mg, 1.95 mmol), in 1,2-dichloroethane (30 mL), was stirred under reflux for 6 hours. The reaction mixture was cooled to room temperature, diluted with chloroform (60 mL) and washed with diluted brine (3 x 50 mL, brine/water, 1:2), dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue was chromatographed using hexane - EtOAc 1:1 as the mobile phase to give a white solid, methyl 6-O-(t-butyldiphenylsilyl)-3-O-(p-chlorobenzoyl)-2-deoxy-2-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethylamino]-1-thio-β-D-glucopyranoside (**4**) (1.1 g, 75%).

Methyl 6-O-(t-butyldiphenylsilyl)-3-O-(p-chlorobenzoyl)-2-deoxy-2-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethylamino]-4-O-tetrahydropyranyl-1-thio-β-D glucopyranoside (5)

A mixture of methyl 6-O-(t-butyldiphenylsilyl)-3-O-(p-chlorobenzoyl)-2-deoxy-2-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethylamino]-1-thio-**β**-D-glucopyranoside (500 mg, 0.6 mmol), 3,4-dihydro-2H-pyran (5 mL) and p-toluenesulphonic acid (5 mg) in dry acetonitrile (10 mL) was stirred at room temperature for 1 hour. The reaction mixture was adjusted to pH 7 with the addition of triethylamine and then evaporated to dryness. The residue was taken up in dichloromethane (30 mL), washed with water (2 x 10 mL) and the organic phase dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue was chromatographed using hexane - EtOAc 2:1 as the mobile phase to give methyl 6-O-(t-butyldiphenylsilyl)-3-O-(p-chlorobenzoyl)-2-deoxy-2-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethylamino]-4-O-tetrahydropyranyl-1-thio-**β**-D-glucopyranoside (**5**)(420 mg, 85%).

Example 3 Synthesis of an Orthogonally Protected Thioglycoside Building Block, methyl 2-azido-6-O-(t-butyldiphenylsilyl)-2-deoxy-3-O-(4-methoxybenzyl)-4-O-biphenylcarbonyl-1-thio-β-D glucopyranoside



Methyl 2-azido-4,6-O-benzylidene-2-deoxy-1-thio-β-D glucopyranoside (7)

A mixture of methyl 2-azido-2-deoxy-1-thio-β-D glucopyranoside (**6**)(10g, 4.25 mmol), α,α-dimethoxytoluene (9.71 g, 64 mmol) and p-toluenesulphonic acid (50 mg) in dry acetonitrile (100 mL), was stirred at 60°C for 2 hours. The reaction mixture was cooled to room temperature and adjusted to pH 7 with the addition of triethylamine. The solvent was removed *in vacuo*. The residue was taken up in CH_2Cl_2 (200 mL), washed with brine (50 mL), with water (50 mL) and dried over $MgSO_4$. The organic phase was concentrated to give a white solid, methyl 2-azido-4,6-O-benzylidene-2-deoxy-1-thio-β-D glucopyranoside (**7**) (10.5 g, 73%).

Methyl 2-azido-4,6-O-benzylidene-2-deoxy-3-O-(4-methoxybenzyl)-1-thio-β-D glucopyranoside (8)

A suspension of sodium hydride (1.0 g, 41.8 mmol) in dry DMF (50 mL) was cooled to 0 °C, and a solution of methyl 2-azido-4,6-O-benzylidene-2-deoxy-1-thio-β-D glucopyranoside (**7**) (9.0 g, 27.8 mmol) in dry DMF (50 mL) was added dropwise in 30 minutes. The resulting solution was stirred at 0 °C for 30 minutes and 4-methoxybenzyl chloride (6.54 g, 41.8 mmol) was added dropwise at 0 °C. The reaction mixture was stirred at room temperature overnight, cooled to 0 °C and dry methanol (5 mL) was added dropwise. The reaction mixture was concentrated under reduced pressure, then xylene (50 mL) was co-evaporated from the residue. The residue was taken up in $CHCl_3$ (200 mL) washed with H_2O (400 ml), saturated $NaHCO_3$ solution (200 mL) dried over $MgSO_4$ and evaporated to dryness. The residue was crystallized from EtOH to give methyl 2-azido-4,6-O-benzylidene-2-deoxy-3-O-(4-methoxybenzyl)-1-thio-β-D-glucopyranoside (**8**) (9,0 g, 73%) as white crystalline solid.

Methyl 2-azido-2-deoxy-3-O-(4-methoxybenzyl)-1-thio-β-D-glucopyranoside (9)

A mixture of methyl 2-azido-4,6-O-benzylidene-2-deoxy-3-O-(4-methoxybenzyl)-1-thio-β-D glucopyranoside (**8**) (12.0 g, 27.08 mmol) and p-toluenesulphonic acid (300 mg) in MeOH - MeCN 1:1 (400 mL) was stirred at 50 C° for 1 hour. The reaction mixture was evaporated, the residue was chromatographed using $CHCl_3$ - EtOAc gradient to give methyl 2-azido-2-deoxy-3-O-(4-methoxybenzyl)-1-thio-β-D-glucopyranoside (**9**) (8.21 g, 88%).

Methyl 2-azido-6-O-tert-butyldiphenylsilyl-2-deoxy-3-O-(4-methoxybenzyl)-1-thio-β-D glucopyranoside (10)

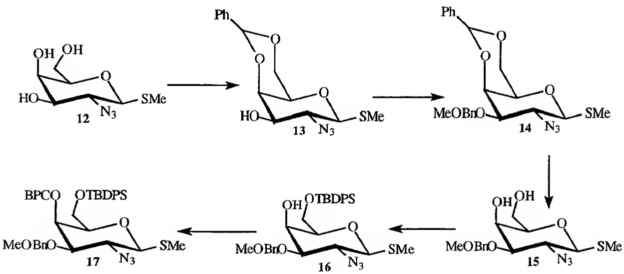
A mixture of t-butyldiphenylsilyl chloride (8.66 g, 31.53 mmol), 4-dimethylaminopyridine (5.12 g, 42.04 mmol) and methyl 2-azido-2-deoxy-3-O-(4-methoxybenzyl)-1-thio-β-D-glucopyranoside (**9**) (7.21 g, 21.02 mmol) in dry 1,2-dichloroethane (100 mL) was stirred at 80°C for 2 hours. The resulting clear solution was cooled to room temperature, diluted with $CHCl_3$ (300 mL), washed with H_2O (3 x 200 mL), brine solution (200 mL), dried over $MgSO_4$ and evaporated. The residue was purified by chromatography using hexane - ether 2:1 as the mobile phase to give methyl 2-azido-6-O-tert-butyldiphenylsilyl-2-deoxy-3-O-(4-methoxybenzyl)-1-thio-β-D glucopyranoside (**10**) (9.73 g, 80%).

Methyl 2-azido-6-O-tert-butyldiphenylsilyl-4-O-biphenylcarbonyl-2-deoxy-3-O-(4-methoxybenzyl)-1-thio-β-D glucopyranoside (11)

A mixture of methyl 2-azido-6-O-tert-butyldiphenylsilyl-2-deoxy-3-O-(4-methoxybenzyl)-1-thio-β-D glucopyranoside (10) (12.7 g, 21.46 mmol), 4-dimethylaminopyridine (5.23 g, 42.92 mmol) in dry 1,2-dichloroethane (100 mL) was stirred at room temperature. Biphenylcarbonyl chloride (6.97 g, 32.19 mmol) was added to the stirred reaction mixture in 15 minutes. After the addition the resulting suspension was stirred under reflux for 3 hours. The reaction mixture was cooled to 10°C and filtered. The crystalline solid was washed on the funnel with dry 1,2-dichloroethane (50 mL) and filtered. The filtrates were combined, diluted with $CHCl_3$ (200 mL) and washed twice with diluted brine solution (water-brine 2:1) (150 mL). The organic layer was dried over $MgSO_4$ and evaporated. The residue was crystallized from EtOH (75 mL) to give methyl 2-azido-6-O-tert-

butyldiphenylsilyl-4-O-biphenylcarbonyl-2-deoxy-3-O-(4-methoxybenzyl)-1-thio-β-D-glucopyranoside (11) (12.7 g, 76%)

Example 4 Synthesis of an Orthogonally Protected Thioglycoside Building Block, methyl 2-azido-6-O-(t-butyldiphenylsilyl)-2-deoxy-3-O-(4-methoxybenzyl)-4-O-biphenylcarbonyl-1-thio-β-D-galactopyranoside (17)



Methyl 2-azido-4,6-O-benzylidene-2-deoxy-1-thio-β-D galactopyranoside (13)

A mixture of methyl 2-azido-2-deoxy-1-thio-β-D-galactopyranoside (**12**)(3.0 g, 12.76 mmol), α,α-dimethoxytoluene (2.91 g, 19.14 mmol) and p-toluenesulphonic acid (30 mg) in dry acetonitrile (15 mL), was stirred at 70ºC for 20 minutes. The reaction mixture was cooled to room temperature and adjusted to pH 7 with the addition of triethylamine. The solvent was removed *in vacuo* and the residue was taken up in CH_2Cl_2 (100 mL), washed with brine (50 mL), with water (50 mL) and dried over $MgSO_4$. The organic phase was concentrated to give a

white solid, methyl 2-azido-4,6-O-benzylidene-2-deoxy-1-thio-β-D-galactopyranoside (**13**) (3.09 g, 75%).

Methyl 2-azido-4,6-O-benzylidene-2-deoxy-3-O-(4-methoxybenzyl)-1-thio-β-D-galactopyranoside (14)

A suspension of sodium hydride (123 mg, 4.87 mmol) in dry DMF (10 mL) was cooled to 0 °C, and a solution of methyl 2-azido-4,6-O-benzylidene-2-deoxy-1-thio-β-D-galactopyranoside (**13**) (1.05 g, 3.25 mmol) in dry DMF (10 mL) was added dropwise in 30 minutes. The resulting solution was stirred at 0 °C for 30 minutes and 4-methoxybenzyl chloride (763 mg, 4.87 mmol) was added dropwise at 0 °C. The reaction mixture was stirred at room temperature overnight, cooled to 0 °C and dry methanol (2 mL) was added dropwise. The reaction mixture was concentrated under reduced pressure, then xylene (25 mL) was co-evaporated from the residue. The residue was taken up in $CHCl_3$ (50 mL) washed with H_2O (40 ml), saturated $NaHCO_3$ solution (50 mL) dried over $MgSO_4$ and evaporated to dryness. The residue was crystallized from EtOH (10 mL)to give methyl 2-azido-4,6-O-benzylidene-2-deoxy-3-O-(4-methoxybenzyl)-1-thio-β-D-galactopyranoside (**14**) (1.0 g, 70%) as white crystalline solid.

Methyl 2-azido-2-deoxy-3-O-(4-methoxybenzyl)-1-thio-β-D-galactopyranoside (15)

A mixture of methyl 2-azido-4,6-O-benzylidene-2-deoxy-3-O-(4-methoxybenzyl)-1-thio-β-D-galactopyranoside (**14**) (500 mg, 1.12 mmol) and p-toluenesulphonic acid (10 mg) in MeOH - MeCN 1:1 (50 mL) was stirred at 50 C° for 1 hour. The reaction mixture was evaporated, the residue was

chromatographed using CHCl3 - EtOAc gradient to give methyl 2-azido-2-deoxy-3-O-(4-methoxybenzyl)-1-thio-β-D-galactopyranoside (**15**) (309 mg, 80%)

Methyl 2-azido-6-O-tert-butyldiphenylsilyl-2-deoxy-3-O-(4-methoxybenzyl)-1-thio-β-D-galactopyranoside (16)

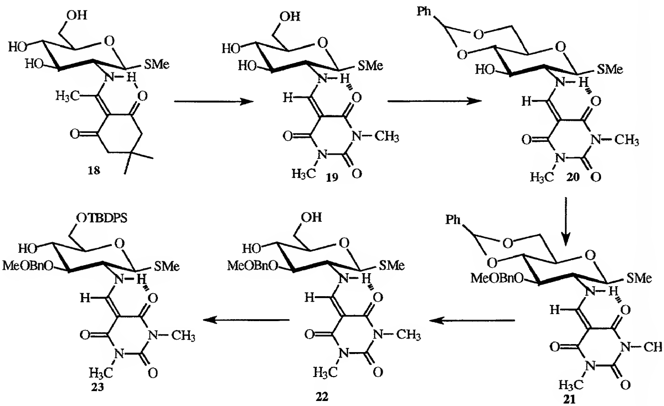
A mixture of t-butyldiphenylsilyl chloride (151 mg, 0.54 mmol), 4-dimethylaminopyridine (90 mg, 0.73 mmol) and methyl 2-azido-2-deoxy-3-O-(4-methoxybenzyl)-1-thio-β-D-galactopyranoside (**15**) (130 mg, 0.36 mmol) in dry 1,2-dichloroethane (8 mL) was stirred at 80°C for 2 hours. The resulting clear solution was cooled to room temperature, diluted with $CHCl_3$ (20 mL), washed with H_2O (3 x 20 mL), brine solution (20 mL), dried over $MgSO_4$ and evaporated. The residue was purified by chromatography using hexane - ether 2:1 as the mobile phase to give methyl 2-azido-6-O-tert-butyldiphenylsilyl-2-deoxy-3-O-(4-methoxybenzyl)-1-thio-β-D-galactopyranoside (**16**) (142 mg, 68%).

Methyl 2-azido-6-O-tert-butyldiphenylsilyl-4-O-biphenylcarbonyl-2-deoxy-3-O-(4-methoxybenzyl)-1-thio-β-D-galactopyranoside (17)

A mixture of methyl 2-azido-6-O-tert-butyldiphenylsilyl-2-deoxy-3-O-(4-methoxybenzyl)-1-thio-β-D-galactopyranoside (**16**) (213 mg, 0.36 mmol), 4-dimethylaminopyridine (67 mg, 0.55 mmol) in dry 1,2-dichloroethane (10 mL) was stirred at room temperature. Biphenylcarbonyl chloride (119 mg, 0.55 mmol) was added to the stirred reaction mixture. The resulting suspension was stirred under reflux for 3 hours. The reaction mixture was cooled to 10°C and filtered. The crystalline solid was washed on the funnel with dry 1,2-dichloroethane (5 mL) and filtered. The filtrates were

combined, diluted with $CHCl_3$ (20 mL) and washed twice with diluted brine solution (water-brine 2:1) (15 mL). The organic layer was dried over $MgSO_4$ and evaporated. The residue was purified by chromatography using hexane - $CHCl_3$ 1:1 as the mobile phase to give methyl 2-azido-6-O-tert-butyldiphenylsilyl-4-O-biphenylcarbonyl-2-deoxy-3-O-(4-methoxybenzyl)-1-thio-β-D-galactopyranoside (**17**) (180 mg, 65%).

Example 5 Synthesis of an Orthogonally Protected Thioglycoside Building Block, Methyl 6-O-(t-butyldiphenylsilyl)-2-deoxy-2-[(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)methylamino]-3-O-(4-methoxybenzyl)-4-O-biphenylcarbonyl-1-thio-β-D-glucopyranoside (23)



Methyl 2-deoxy-2-[(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)methylamino]-1-thio-β-D-glucopyranoside (19)

To methyl 2-deoxy-2-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)-ethylamino]-1-thio-β-D-glucopyranoside (**18**)(100 g, 268 mmol) was added conc. ammonia solution (300 mL) and the reaction mixture was stirred at 100 C° for 1 hour. The suspension was cooled to room temperature and filtered. The filtrate was washed with $CHCl_3$ (3x200 mL), then the aqueous phase was evaporated under reduced pressure. The residue was taken up in EtOH : benzene 1:1 (250 mL) and evaporated to dryness.

The residue was taken up in hot MeOH (600 mL) and 1, 3-dimethyl-5-[(dimethylamino)methylene]2, 4, 6 (1H, 3H, 5H)-trioxopyrimidine (Wow-reagent) (62.27 g, 294.9 mmol) in hot MeOH (120 mL) was added. /Synthesis of 1, 3-Dimethyl-5-[(dimethylamino)methylene]2, 4, 6 (1H, 3H, 5H)-trioxopyrimidine (Wow-reagent): N, N-Dimethylformamide dimethyl acetal (252 g, 2.11 mol) was stirred at 0°C in $CHCl_3$ (750 mL). 1, 3-Dimethylbarbituric acid (300 g, 1.92 mol) in $CHCl_3$ (2100 mL) was added to the stirring acetal solution over 2 hours. The $CHCl_3$ was evaporated immediately following complete addition and the resulting residue re-suspended in $CHCl_3$ (2000 mL) and washed with water (3x600 mL) and saturated brine solution (600 mL). The organic phase was dried over $MgSO_4$, filtered and evaporated to dryness under high vacuum. The residue was re-suspended in diethyl ether (750 mL), filtered and washed on the funnel with additional diethyl ether (500 mL) to yield 1, 3-Dimethyl-5-[(dimethylamino)methylene]2, 4, 6 (1H, 3H, 5H)-trioxopyrimidine as a pale-yellow solid (271.85 g, 67%)./ The reaction mixture was stirred under reflux for 30 minutes, then cooled to room temperature. The resulting suspension was filtered, the solid was washed with MeOH (150 mL), ether (150 mL), dried to give methyl 2-deoxy-2-[(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-

ylidene)methylamino]-1-thio-β-D-glucopyranoside (**19**)(83 g, 90%).

Methyl 4,6-O-benzylidene-2-deoxy-2-[(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)methylamino]-1-thio-β-D-glucopyranoside (20)

A mixture of methyl 2-deoxy-2-[(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)methylamino]-1-thio-β-D-glucopyranoside (19)(84.64 g, 226.31 mmol), α,α-dimethoxytoluene (51.66 g, 339.46 mmol) and p-toluenesulphonic acid (500 mg) in dry acetonitrile (600 mL), was stirred at 60ºC for 2 hours. The reaction mixture was cooled to room temperature and filtered. The solid was washed with ether (200 mL), dried to give methyl 4,6-O-benzylidene-2-deoxy-[(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)methylamino]-1-thio-β-D-glucopyranoside (**20**) (80 g, 77%).

Methyl 4,6-O-benzylidene-2-deoxy-2-[(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)methylamino]-3-O-(4-methoxybenzyl)-1-thio-β-D-glucopyranoside (21)

A suspension of sodium hydride (6.82 g, 269.97 mmol) in dry DMF (50 mL) was cooled to 0 °C, and a solution of methyl 4,6-O-benzylidene-2-deoxy-2-[(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)methylamino]-1-thio-β-D-glucopyranoside (**20**) (50 g, 107.99 mmol in dry DMF (200 mL) was added dropwise in 30 minutes. The resulting solution was stirred at room temperature for 30 minutes and 4-methoxybenzyl chloride (37.36 g, 238.56 mmol) was added dropwise at 0 °C. The reaction mixture was stirred at room temperature overnight, cooled to 0 °C and dry methanol (10 mL) was added dropwise. The reaction mixture was

concentrated under reduced pressure, then xylene (200 mL) was co-evaporated from the residue. The residue was taken up in $CHCl_3$ (1000 mL) washed with H_2O (1000 ml), saturated $NaHCO_3$ solution (1000 mL) dried over $MgSO_4$ and evaporated to dryness. The residue was crystallized from EtOH to give methyl 4,6-O-benzylidene-2-deoxy-2-[(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)methylamino]-3-O-(4-methoxybenzyl)-1-thio-β-D-glucopyranoside (**21**) (52.21 g, 82%).

Methyl 2-deoxy-2-[(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)methylamino]-3-O-(4-methoxybenzyl)-1-thio-β-D-glucopyranoside (22)

A mixture of methyl 4,6-O-benzylidene-2-deoxy-2-[(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)methylamino]-3-O-(4-methoxybenzyl)-1-thio-β-D-glucopyranoside (**21**) (52.21 g, 89.55 mmol and p-toluenesulphonic acid (200 mg) in MeOH - MeCN 1:1 (400 mL) was stirred at 50 C° for 1 hour. The reaction mixture was evaporated, the residue was chromatographed using CHCl3 - MeOH 10:1 as the mobile phase to give methyl 2-deoxy-2-[(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)methylamino]-3-O-(4-methoxybenzyl)-1-thio-β-D-glucopyranoside (**22**) (31.0 g, 70%)

Methyl 6-O-tert-butyldiphenylsilyl-2-deoxy-2-[(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)methylamino]-3-O-(4-methoxybenzyl)-1-thio-β-D-glucopyranoside (23)

A mixture of t-butyldiphenylsilyl chloride (16.65 g, 60.60 mmol), 4-dimethylaminopyridine (9.85 g, 80.80 mmol) and methyl 2-deoxy-2-[(1,3-dimethyl-2,4,6(1H,3H,5H)-

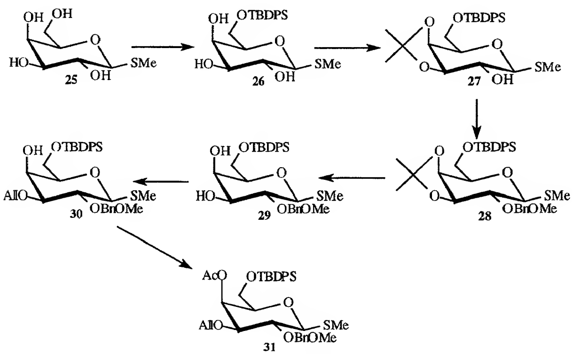
trioxopyrimidin-5-ylidene)methylamino]-3-O-(4-methoxybenzyl)-1-thio-β-D-glucopyranoside (**22**) (20 g, 40.4 mmol) in dry 1,2-dichloroethane (200 mL) was stirred at 80°C for 2 hours. The resulting clear solution was cooled to room temperature, diluted with $CHCl_3$ (200 mL), washed with H_2O (3 x 500 mL), brine solution (500 mL), dried over $MgSO_4$ and evaporated. The residue was purified by chromatography using 1,2-dichloroethane - EtOAc 10:1 as the mobile phase to give methyl 6-O-tert-butyldiphenylsilyl-2-deoxy-2-[(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)methylamino]-3-O-(4-methoxybenzyl)-1-thio-β-D-glucopyranoside (**23**) (23.3 g, 79%).

Methyl 6-O-tert-butyldiphenylsilyl-4-O-biphenylcarbonyl-2-deoxy-2-[(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)methylamino]-3-O-(4-methoxybenzyl)-1-thio-β-D-glucopyranoside (24)

A mixture of methyl 6-O-tert-butyldiphenylsilyl-2-deoxy-2-[(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)methylamino]-3-O-(4-methoxybenzyl)-1-thio-β-D-glucopyranoside (**23**) (10.0 g, 13.64 mmol), 4-dimethylaminopyridine (2.5 g, 20.46 mmol) in dry 1,2-dichloroethane (100 mL) was stirred at room temperature. Biphenylcarbonyl chloride (4.42 g, 20.46 mmol) was added to the stirred reaction mixture. The resulting suspension was stirred under reflux for 3 hours. The reaction mixture was cooled to 10°C and filtered. The crystalline solid was washed on the funnel with dry 1,2-dichloroethane (20 mL) and filtered. The filtrates were combined, diluted with $CHCl_3$ (100 mL) and washed twice with diluted brine solution (water-brine 2:1) (150 mL). The organic layer was dried over $MgSO_4$ and evaporated. The residue was purified by chromatography using hexane - $CHCl_3$ 1:1 as the mobile phase to give methyl 6-O-tert-butyldiphenylsilyl-4-O-

biphenylcarbonyl-2-deoxy-2-[(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)methylamino]-3-O-(4-methoxybenzyl)-1-thio-β-D-glucopyranoside (**24**) (9.5 g, 75%).

Example 6 Synthesis of an Orthogonally Protected Thioglycoside Building Block, Methyl 6-*O*-(*t*-butyldiphenylsilyl)-2-*O*-(4-methoxybenzyl)-3-*O*-allyl-4-*O*-acetyl-1-thio-β-D-galactopyranoside (6)



Methyl 6-*O*-(*t*-butyldiphenylsilyl)-1-thio-β-D-galactopyranoside (26)

A mixture of methyl 1-thio-β-D-galactopyranoside (**25**) (5 g, 28 mmol), chloro *t*-butyldiphenylsilane (5.85 g, 21 mmol) and DMAP (2.63 g, 21 mmol) in dry 1, 2-dichloroethane (130 mL) was left to stir at reflux for 2.5 h. The reaction mixture was cooled to room temperature, diluted with dichloromethane (200 mL) and washed with saturated sodium chloride solution (2 x 250 mL). The organic phase was dried over $MgSO_4$ and subsequently evaporated to dryness to

give methyl 6-*O*-(*t*-butyldiphenylsilyl)-1-thio-β-D-galactopyranoside (**26**) (7.5 g, 81%) as a colorless oil.

Methyl 6-*O*-(*t*-butyldiphenylsilyl)-3,4-*O*-isopropylidene-1-thio-β-D-galactopyranoside (27)

A mixture of methyl 6-*O*-(*t*-butyldiphenylsilyl)-1-thio-β-D-galactopyranoside (**26**) (7.4 g, 16.5 mmol) and *p*-toluenesulphonic acid (20 mg) in 2,2-dimethoxypropane (100 mL) was left to stir at room temperature for 2 h. The reaction mixture was then neutralized with triethylamine (1 mL) and evaporated to dryness. The residue was dissolved in dichloromethane (250 mL), washed with water (1 x 250 mL), dried over $MgSO_4$ and evaporated to dryness to give methyl 6-*O*-(*t*-butyldiphenylsilyl)-3,4-*O*-isopropylidene-1-thio-β-D-galactopyranoside (**27**) (7.0 g, 87%) as a white solid.

Methyl 6-*O*-(*t*-butyldiphenylsilyl)-2-*O*-(4-methoxybenzyl)-3,4-*O*-isopropylidene-1-thio-β-D-galactopyranoside (28)

To a suspension of sodium hydride (95%, 0.53 g, 21 mmol) in dry DMF (100 mL) at 0° C°, was added dropwise methyl 6-*O*-(*t*-butyldiphenylsilyl)-3,4-*O*-isopropylidene-1-thio-β-D-galactopyranoside (**27**) (6.8 g, 13.9 mmol) as a solution in dry DMF (25 mL) in 5 minutes. The resulting mixture was left to stir at 0 C° for 15 min and then at room temperature for 1 h. The mixture was then cooled to 0 C° and a solution of 4-methoxybenzyl chloride (3.27 g, 21 mmol) in dry DMF (25 mL) was added dropwise, over 5 min. The reaction mixture was left to stir at 0° C for 15 min and then at room temperature for 16 h. After this period the reaction was neutralized with absolute ethanol (15 mL) at 0° C, and then evaporated to dryness. The residue was taken up in chloroform (400 mL), washed with water (300 mL)

and saturated sodium bicarbonate solution (300 mL). The organic phase was dried over $MgSO_4$ and evaporated to dryness to give the crude product as an orange oil (~9 g). The crude material was chromatographed using EtOAc - hexane 25 : 75 as the mobile phase to give methyl 6-*O*-(*t*-butyldiphenylsilyl)-2-*O*-(4-methoxybenzyl)-3,4-*O*-isopropylidene-1-thio-β-D-galactopyranoside (**28**) as a pale yellow oil (6.5 g, 77%).

Methyl 6-*O*-(*t*-butyldiphenylsilyl)-2-*O*-(4-methoxybenzyl)-1-thio-β-D-galactopyranoside (29)

A suspension of methyl 6-*O*-(*t*-butyldiphenylsilyl)-2-*O*-(4-methoxybenzyl)-3,4-*O*-isopropylidene-1-thio-β-D-galactopyranoside (**28**) (6.4 g, 10.5 mmol) in acetic acid (80%, 150 mL) was left to stir at 70 C° for 1.5 h. The reaction mixture was evaporated to dryness and the remaining residue was chromatographed using EtOAc - hexane 1 : 1) to give methyl 6-*O*-(*t*-butyldiphenylsilyl)-2-*O*-(4-methoxybenzyl)-1-thio-β-D-galactopyranoside (**29**) as a pale yellow oil (3.0 g, 50%).

Methyl 6-*O*-(*t*-butyldiphenylsilyl)-2-*O*-(4-methoxybenzyl)-3-*O*-allyl-1-thio-β-D-galactopyranoside (30)

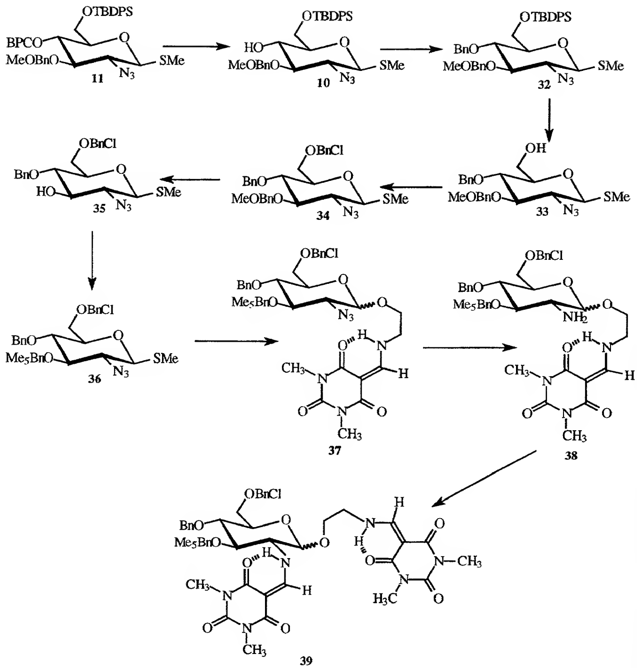
A mixture of methyl 6-*O*-(*t*-butyldiphenylsilyl)-2-*O*-(4-methoxybenzyl)-1-thio-β-D-galactopyranoside (**29**) (2.8 g, 4.9 mmol) and dibutyl tin oxide (1.6 g, 6.4 mmol) in anhydrous methanol (200 mL) was stirred at reflux for 1 h. The reaction mixture was evaporated to dryness and the remaining residue dissolved in dry toluene (50 mL). Tetraethylammonium bromide (1.34 g, 6.4 mmol) and allyl bromide (7.7 g, 64 mmol) were added. The reaction mixture was left to stir at reflux overnight. The reaction mixture

was cooled to room temperature and filtered. The filtrate was evaporated to dryness and the residue was purified by chromatography using EtOAc - hexane 15 : 85 as the mobile phase to give methyl 6-*O*-(*t*-butyldiphenylsilyl)-2-*O*-(4-methoxybenzyl)-3-*O*-allyl-1-thio-β-D-galactopyranoside (**30**) (1.5 g, 50%) as a pale yellow oil.

Methyl 6-*O*-(*t*-butyldiphenylsilyl)-2-*O*-(4-methoxybenzyl)-3-*O*-allyl-4-*O*-acetyl-1-thio-β-D-galactopyranoside (31)

To a solution of methyl 6-*O*-(*t*-butyldiphenylsilyl)-2-*O*-(4-methoxybenzyl)-3-*O*-allyl-1-thio-β-D-galactopyranoside (**30**) (1.4 g, 2.3 mmol) in pyridine (30 mL) was added acetic anhydride (20 g, 196 mmol) in one portion. The resulting solution was left to stir at room temperature for 72 h. The reaction contents were then evaporated to dryness and the residue was dissolved in dichloromethane (200 mL). The solution was washed with potassium hydrogen sulphate solution (1M, 2 x 150 mL) followed by saturated sodium chloride (150 mL), dried over $MgSO_4$ and evaporated to dryness. The crude residue was purified by chromatography using dichloromethane as the mobile phase to give Methyl 6-*O*-(*t*-butyldiphenylsilyl)-2-*O*-(4-methoxybenzyl)-3-*O*-allyl-4-*O*-acetyl-1-thio-β-D-galactopyranoside (**31**) (750 mg, 48%) as a pale yellow oil.

Example 7 Selective Deprotection - Etherification study using an Orthogonally Protected Thioglycoside Building Block, Methyl 2-azido-6-O-tert-butyldiphenylsilyl-4-O-biphenylcarbonyl-2-deoxy-3-O-(4-methoxybenzyl)-1-thio-β-D glucopyranoside (11)



Methyl 2-azido-6-O-tert-butyldiphenylsilyl-2-deoxy-3-O-(4-methoxybenzyl)-1-thio-β-D-glucopyranoside (10)

Sodium (89 mg) was reacted in dry MeOH (50 mL)then a solution of methyl 2-azido-4-O-biphenylcarbonyl-6-O-tert-butyldiphenylsilyl-2-deoxy-3-O-(4-methoxybenzyl)-1-thio-β-D-glucopyranoside (**11**) (3 g, 3.88 mmol) in THF (25 mL) was added. The reaction mixture was stirred at 40 C° for 30 minutes, then cooled to room temperature. The solution was

neutralized by Amberlite IR 120 (H^+) ion exchange resin. The suspension was filtered, the filtrate was evaporated. The residue was purified by chromatography using EtOAc - hexane 1 : 4 as the mobile phase to give methyl 2-azido-6-O-tert-butyldiphenylsilyl-2-deoxy-3-O-(4-methoxybenzyl)-1-thio-β-D-glucopyranoside (**10**) (2.1 g, 91%)

Methyl 2-azido-4-O-benzyl-6-O-tert-butyldiphenylsilyl-2-deoxy-3-O-(4-methoxybenzyl)-1-thio-β-D-glucopyranoside (32)

A suspension of sodium hydride (196 mg, 5.1 mmol) in dry DMF (10 mL) was cooled to 0 °C, and a solution of methyl 2-azido-6-O-tert-butyldiphenylsilyl-2-deoxy-3-O-(4-methoxybenzyl)-1-thio-β-D glucopyranoside (**10**) (2.53 g, 4.3 mmol) in dry DMF (20 mL) was added dropwise in 30 minutes. The resulting solution was stirred at room temperature for 30 minutes and benzyl bromide (880 mg, 5.1 mmol) was added dropwise at 0 °C. The reaction mixture was stirred at room temperature overnight, cooled to 0 °C and dry methanol (1 mL) was added dropwise. The reaction mixture was concentrated under reduced pressure, then xylene (20 mL) was co-evaporated from the residue. The residue was taken up in $CHCl_3$ (100 mL) washed with H_2O (100 ml), saturated $NaHCO_3$ solution (100 mL) dried over $MgSO_4$ and evaporated to dryness. The residue was purified by chromatography using EtOAc - Hexane 1 : 9 as the mobile phase to give methyl 2-azido-4-O-benzyl-6-O-tert-butyldiphenylsilyl-2-deoxy-3-O-(4-methoxybenzyl)-1-thio-β-D-glucopyranoside (**32**) (2.0 g, 68%).

Methyl 2-azido-4-O-benzyl-2-deoxy-3-O-(4-methoxybenzyl)-1-thio-β-D-glucopyranoside (33)

To a mixture of methyl 2-azido-4-O-benzyl-6-O-tert-butyldiphenylsilyl-2-deoxy-3-O-(4-methoxybenzyl)-1-thio-β-D-glucopyranoside (**32**) (1.5 g, 2.2 mmol) and anhydrous AcOH (28.8 mL) in dry THF (169 mL) hydrogen fluoride-pyridine complex (20.3 mL) was added in a polypropylene container. The reaction mixture was kept at room temperature

overnight, then diluted with EtOAc (1 L). The resulting solution was washed with saturated sodium hydrogen carbonate (4 x 1 L), saturated brine solution (1 L), dried over $MgSO_4$ and evaporated to dryness. The residue was crystallized from MeOH. The mother liquor was evaporated, the residue was treated with hexane to get more solid. The solid products were combined affording methyl 2-azido-4-O-benzyl-2-deoxy-3-O-(4-methoxybenzyl)-1-thio-β-D-glucopyranoside (**33**) (735 mg, 75%).

Methyl 2-azido-4-O-benzyl-6-O-(4-chlorobenzyl)-2-deoxy-3-O-(4-methoxybenzyl)-1-thio-β-D-glucopyranoside (34)

A suspension of sodium hydride (71 mg, 1.8 mmol) in dry DMF (5 mL) was cooled to 0 °C, and a solution of methyl 2-azido-4-O-benzyl-2-deoxy-3-O-(4-methoxybenzyl)-1-thio-β-D-glucopyranoside (**33**) (680 mg, 1.5 mmol) in dry DMF (5 mL) was added dropwise in 30 minutes. The resulting solution was stirred at room temperature for 30 minutes and 4-chlorobenzyl chloride (295 mg, 1.5 mmol) was added dropwise at 0 °C. The reaction mixture was stirred at room temperature for 4.5 hours, cooled to 0 °C and dry methanol (1 mL) was added dropwise. The reaction mixture was concentrated under reduced pressure, then xylene (10 mL) was co-evaporated from the residue. The residue was treated with hexane (10 mL) and filtered to give methyl 2-azido-4-O-benzyl-6-O-(4-chlorobenzyl)-2-deoxy-3-O-(4-methoxybenzyl)-1-thio-β-D-glucopyranoside (**34**) (620 mg, 71 %).

Methyl 2-azido-4-O-benzyl-6-O-(4-chlorobenzyl)-2-deoxy-1-thio-β-D-glucopyranoside (35)

A mixture of methyl 2-azido-4-O-benzyl-6-O-(4-chlorobenzyl)-2-deoxy-3-O-(4-methoxybenzyl)-1-thio-β-D glucopyranoside (**34**) (580 mg, 1.01 mmol) and DDQ (270 mg, 1.2 mmol) in CH_2Cl_2 - H_2O 9:1 (10 mL) was stirred at room temperature for 3 hours. The reaction mixture was washed with saturated $NaHCO_3$ solution (3 x 15 ml), dried over

$MgSO_4$ and evaporated. The residue was purified by chromatography using $CHCl_3$-Hexane-MeOH 30:20:0.5 as the mobile phase to give methyl 2-azido-4-O-benzyl-6-O-(4-chlorobenzyl)-2-deoxy-1-thio-β-D glucopyranoside (**35**) (300 mg, 66%).

Methyl 2-azido-4-O-benzyl-6-O-(4-chlorobenzyl)-2-deoxy-3-O-pentamethylbenzyl-1-thio-β-D-glucopyranoside (36)

A suspension of sodium hydride (40 mg, 1.0 mmol, 60%) in dry DMF (5 mL) was cooled to 0 °C, and a solution of methyl 2-azido-4-O-benzyl-6-O-(4-chlorobenzyl)-2-deoxy-1-thio-β-D glucopyranoside (**35**) (280 mg, 0.67 mmol) in dry DMF (5 mL) was added dropwise in 30 minutes. The resulting solution was stirred at room temperature for 30 minutes and pentamethylbenzyl chloride (200 mg, 1.0 mmol) was added dropwise at 0 °C. The reaction mixture was stirred at room temperature for 4 hours, cooled to 0 °C and dry methanol (1 mL) was added dropwise. The reaction mixture was concentrated under reduced pressure then xylene (10 mL) was co-evaporated from the residue. The residue was in EtOAc (100 mL), washed with brine (2 x 100 mL), dried over $MgSO_4$ and evaporated. The resulting solid was suspended in hexane (50 mL)and filtered to give methyl 2-azido-4-O-benzyl-6-O-(4-chlorobenzyl)-2-deoxy-3-O-pentamethylbenzyl-1-thio-β-D-glucopyranoside (**36**) (290 mg, 76%).

2-[(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)methylamino]-ethyl 2-azido-4-O-benzyl-6-O-(4-chlorobenzyl)-2-deoxy-3-O-pentamethylbenzyl-α,β-D-glucopyranoside (37)

A mixture of methyl 2-azido-4-O-benzyl-6-O-(4-chlorobenzyl)-2-deoxy-3-O-pentamethylbenzyl-1-thio-β-D glucopyranoside (**36**) (220 mg, 0.36 mmol), 2-[(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)methylamino]-ethanol (150 mg, 0.66 mmol), molecular sieves 4A (1 g) and DMTST (138 mg, 0.66 mmol) in 1,2-dichloroethane (10 mL) was stirred at room temperature for 30 minutes. The reaction

mixture was neutralized with TEA (0.5 mL) and evaporated. The residue was purified by chromatography using $CHCl_3$-MeOH 40 mL : 20 drops as the mobile phase to give 2-[(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)methylamino]-ethyl 2-azido-4-O-benzyl-6-O-(4-chlorobenzyl)-2-deoxy-3-O-pentamethylbenzyl-β-D glucopyranoside (**37**) (220 mg, 77%).

2-[(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)methylamino]-ethyl 2-amino-4-O-benzyl-6-O-(4-chlorobenzyl)-2-deoxy-3-O-pentamethylbenzyl-α,β-D-glucopyranoside (38)

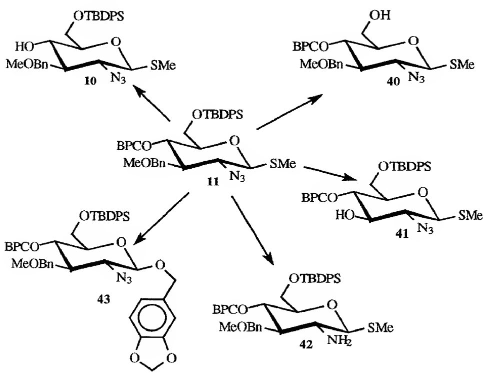
A mixture of 2-[(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)methylamino]-ethyl 2-azido-4-O-benzyl-6-O-(4-chlorobenzyl)-2-deoxy-3-O-pentamethylbenzyl-β-D glucopyranoside (**37**) (160 mg, 0.2 mmol) and TEA (3 drops) in 1,3-propanedithiol (1 mL) was stirred at room temperature overnight. The reaction mixture was chromatographed using EtOAc - hexane 1:1 then EtOAc - MeOH 10:1 solvent systems as mobile phases to give 2-[(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)methylamino]-ethyl 2-amino-4-O-benzyl-6-O-(4-chlorobenzyl)-2-deoxy-3-O-pentamethylbenzyl-α,β-D glucopyranoside (**38**) (123 mg, 80%)

2-[(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)methylamino]-ethyl 2-[(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)methylamino]-4-O-benzyl-6-O-(4-chlorobenzyl)-2-deoxy-3-O-pentamethylbenzyl-α,β-D glucopyranoside (39)

A mixture of 2-[(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)methylamino]-ethyl 2-amino-4-O-benzyl-6-O-(4-chlorobenzyl)-2-deoxy-3-O-pentamethylbenzyl-β-D glucopyranoside (**38**) (50 mg, 0.066 mmol), 1,3-dimethyl-5-[(dimethylamino)methylene]2,4,6(1H,3H,5H)-trioxopyrimidine (Wow-reagent) (50 mg, 0.24 mmol), TEA (0.2 mL) in $CHCl_3$ - MeOH 3:1 (4 mL) was stirred at room

temperature for 3 hours. The reaction mixture was evaporated, the resulting residue was chromatographed using EtOAc as the mobile phase to give 2-[(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)methylamino]-ethyl 2-[(1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidin-5-ylidene)methylamino]-4-O-benzyl-6-O-(4-chlorobenzyl)-2-deoxy-3-O-pentamethylbenzyl-α,β-D glucopyranoside (**39**) (45 mg, 75%).

Example 8 **Selective deprotection study using an Orthogonally Protected Thioglycoside Building Block, Methyl 2-azido-6-O-tert-butyldiphenylsilyl-4-O-biphenylcarbonyl-2-deoxy-3-O-(4-methoxybenzyl)-1-thio-β-D glucopyranoside (11)**



Methyl 2-azido-6-O-tert-butyldiphenylsilyl-2-deoxy-3-O-(4-methoxybenzyl)-1-thio-β-D glucopyranoside (10)

Sodium (89 mg) was reacted in dry MeOH (50 mL)then a solution of methyl 2-azido-4-O-biphenylcarbonyl-6-O-tert-butyldiphenylsilyl-2-deoxy-3-O-(4-methoxybenzyl)-1-thio-β-D

glucopyranoside (**11**) (3 g, 3.88 mmol) in THF (25 mL) was added. The reaction mixture was stirred at 40 C° for 30 minutes, then cooled to room temperature. The solution was neutralized by Amberlite IR 120 (H^+) ion exchange resin. The suspension was filtered, the filtrate was evaporated. The residue was purified by chromatography using EtOAc - hexane 1 : 4 as the mobile phase to give methyl 2-azido-6-O-tert-butyldiphenylsilyl-2-deoxy-3-O-(4-methoxybenzyl)-1-thio-β-D glucopyranoside (**10**) (2.1 g, 91%).

Methyl 2-azido-4-O-biphenylcarbonyl-2-deoxy-3-O-(4-methoxybenzyl)-1-thio-β-D-glucopyranoside (40)

To a mixture of methyl 2-azido-4-O-biphenylcarbonyl-6-O-tert-butyldiphenylsilyl-2-deoxy-3-O-(4-methoxybenzyl)-1-thio-β-D-glucopyranoside (**11**) (150 mg, 0.19 mmol) and anhydrous AcOH (2.8 mL) in dry THF (17 mL) hydrogenfluoride-pyridine complex (2 mL) was added in a polypropylene container. The reaction mixture was kept at room temperature overnight, then diluted with EtOAc (100 mL). The resulting solution was washed with saturated sodiumhydrogen carbonate (4 x 100 mL), saturated brine solution (100 mL), dried over $MgSO_4$ and evaporated to dryness. The residue was purified by chromatography using EtOAc - hexane 2:5 as the mobile phase to give methyl 2-azido-4-O-biphenylcarbonyl-2-deoxy-3-O-(4-methoxybenzyl)-1-thio-β-D-glucopyranoside (**40**) (96 mg, 93%).

Methyl 2-azido-4-O-biphenylcarbonyl-6-O-tert-butyldiphenylsilyl-2-deoxy-1-thio-β-D-glucopyranoside (41)

A mixture of methyl 2-azido-4-O-biphenylcarbonyl-6-O-tert-butyldiphenylsilyl-2-deoxy-3-O-(4-methoxybenzyl)-1-thio-β-D-glucopyranoside (**11**) (150 mg, 0.19 mmol) and DDQ (52 mg, 0.23 mmol) in CH_2Cl_2 - H_2O 9:1 (5 mL) was stirred at room temperature for 3 hours. The reaction mixture was washed with saturated $NaHCO_3$ solution (3 x 3 ml), dried over $MgSO_4$ and evaporated. The residue was purified by chromatography using EtOAc - hexane 15:85 as the mobile phase to give

methyl 2-azido-4-O-biphenylcarbonyl-6-O-tert-butyldiphenylsilyl-2-deoxy-1-thio-β-D-glucopyranoside (**41**) (116 mg, 92%).

Methyl 2-amino-4-O-biphenylcarbonyl-6-O-tert-butyldiphenylsilyl-2-deoxy-3-O-(4-methoxybenzyl)-1-thio-β-D-glucopyranoside (42)

A mixture of methyl 2-azido-4-O-biphenylcarbonyl-6-O-tert-butyldiphenylsilyl-2-deoxy-3-O-(4-methoxybenzyl)-1-thio-β-D-glucopyranoside (**11**) (150 mg, 0.19 mmol) and TEA (3 drops) in 1,3-propanedithiol (1 mL) was stirred at room temperature overnight. The reaction mixture was chromatographed using EtOAc - hexane 15:85 then EtOAc - hexane 1:1 solvent systems as mobile phases to give methyl 2-amino-4-O-biphenylcarbonyl-6-O-tert-butyldiphenylsilyl-2-deoxy-3-O-(4-methoxybenzyl)-1-thio-β-D-glucopyranoside (**42**) (130 mg, 91%).

3,4-Methylenedioxybenzyl 2-azido-4-O-biphenylcarbonyl-6-O-tert-butyldiphenylsilyl-2-deoxy-3-O-(4-methoxybenzyl)-α,β-D-glucopyranoside (43)

A mixture of methyl 2-azido-4-O-biphenylcarbonyl-6-O-tert-butyldiphenylsilyl-2-deoxy-3-O-(4-methoxybenzyl)-1-thio-β-D-glucopyranoside (**11**) (200 mg, 0.26 mmol), 3,4-methylenedioxybenzyl alcohol 59 mg, 0.39 mmol), molecular sieves 4A (1 g) and methyltriflate (106 mg, 0.65 mmol) in 1,2-dichloroethane (10 mL) was stirred at room temperature overnight. The reaction mixture was neutralized with TEA (0.5 mL) and evaporated. The residue was purified by chromatography using EtOAc - hexane 15:85 as the mobile phase to give 3,4-methylenedioxybenzyl 2-azido-4-O-biphenylcarbonyl-6-O-tert-butyldiphenylsilyl-2-deoxy-3-O-(4-methoxybenzyl)-α,β-D-glucopyranoside (**43**) (173 mg, 76%).

It will be apparent to the person skilled in the art that while the invention has been described in some detail for the purposes of clarity and understanding,

various modifications and alterations to the embodiments and methods described herein may be made without departing from the scope of the inventive concept disclosed in this specification.

References cited herein are listed below, and are incorporated herein by this reference.

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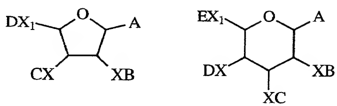
CLAIMS

1. A universal monosaccharide building block of General Formula I or General Formula II



I II

in which

A is a leaving group;

X is hydrogen, O, N or N_3;

X_1 is hydrogen, $-CH_2O-$, $-CH_2NH-$, $-CH_3$, $-CH_2N_3$ or -COO-; and

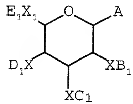
B, C, D and E are protecting groups which can be cleaved orthogonally,

and in which

B, C, D and E are absent when X is hydrogen or N_3, and E is absent when X_1 is hydrogen, CH_3 or N_3.

2. A monosaccharide building block according to claim 1, in which A is selected from the group consisting of -SR; where R is alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, halogen; trichloroacetimidoyl-; sulphoxide; and -O-alkenyl.

3. A monosaccharide building block according to claim 1 or claim 2, which is a compound of General Formula III

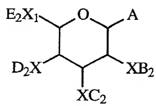


III

in which

B_1, C_1, D_1 and E_1 are orthogonal carbohydrate protecting groups selected from protecting group sets 1, 2, 6 and 8 as herein defined.

4. A monosaccharide building block according to claim 1 or claim 2, which is a compound of General Formula IV



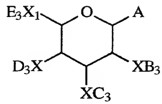
IV

in which

B_2, C_2, D_2 and E_2 are selected from the members of protecting group set 1, and in themselves constitute an orthogonal set.

5. A monosaccharide building block according to claim 4, in which the members of protecting group set 1 are levanoyl, chloroacetate, *p*-methoxybenzyloxycarbonyl and 2-trimethylsilylethylcarbonate.

6. A monosaccharide building block according to claim 1 or claim 2, which is a compound of General Formula V



V

in which

A, X and X_1 are as defined for General Formula I and II, and

B_3, C_3, D_3 and E_3 are an orthogonal set of protecting groups selected from amongst the members of set 1 and from the remaining orthogonal sets.

7. A method of synthesis of a molecule selected from the group consisting of glycoconjugates of non-carbohydrate molecules, neo-glycoconjugates and oligosaccharides, comprising the step of using a monosaccharide building block according to any one of claims 1 to 6.

8. A method according to claim 7, in which the molecule comprises one or more compounds in which substituents are linked to a pyranose or furanose ring.

9. A method according to claim 7 or claim 8, in which the molecule comprises a sugar analogue.

10. A method according to any one of claims 7 to 9, in which the synthesis is carried out in solution.

11. A method according to any one of claims 7 to 9, in which the synthesis is carried out on a solid-phase support.

As a below named joint inventor, each of us hereby declares as follows:

My residence, post office address and citizenship are as stated below next to my name.

I believe that I am an original, first, and joint inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled:

PROTECTING GROUPS FOR CARBOHYDRATE SYNTHESIS

The specification of which was filed in the U.S. Patent and Trademark Office on 18 July 2001 and assigned application serial No. 09/889,687.

We hereby claim the benefit under 35 U.S.C. § 365 (c) of any PCT international application designating the US, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior PCT international application in the manner provided by the first paragraph of 35 U.S.C. § 112, we acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56 which became available between the filing date of the prior application and the PCT international filing date of this application:

PCT international application number: PCT/AU00/00025, filed July 18, 2000.

We hereby claim foreign priority benefits under 35 U.S.C. §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Australian Patent Application No. PP8230, filed January 18, 1999

I acknowledge the duty to disclose information of which I am aware that is material to the examination of this application in accordance with 37 C.F.R. §1.56(a). That, as to the subject matter of this application , I do not know and do not believe: that this invention was ever known or used in the United States of America before my invention thereof; that this invention was patented or described in any printed publication in any country before my invention thereof or more than one year prior to said application; that this invention was in public use or on sale in the United States of America more than one year prior to said application; that this invention has been patented or made the subject of an inventor's certificate issued before the date of said application in any country foreign to the United States of America on an application filed by me or my legal representatives or assigns more than twelve months prior to said application; nor that any application for patent or inventor's certificate on this invention has been filed in any country foreign to the United States of America prior to said application by me or my legal

representatives or assigns, except for PCT international patent application No. PCT/AU00/00025, filed July 18, 2000 or Australian Patent Application No. PP8230, filed January 18, 1999.

We hereby appoint the following attorneys to prosecute this application and to transact all business in the United States Patent and Trademark Office connected therewith:

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We hereby declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

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